

### **III. Discussion of the Restriction Requirement**

A restriction requirement has been imposed on the pending claims.

By this amendment, R<sup>1</sup> and R<sup>2</sup> have been limited to forming in combination, together with an adjacent nitrogen atom, a 1-piperidinyl ring optionally having a substituent or substituents in independent claims 1, 26 and 27. In conjunction with these changes, dependent claims 5, 7, 32 and 34 have also been modified and claims 4, 6, 31 and 33 have been cancelled.

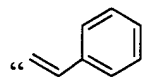
Therefore Applicants respectfully assert that the pending claims as amended are in accordance with the restriction requirement.

#### IV. Discussion of the Objections to the Specification

The specification has been objected to as allegedly containing new matter by virtue of the previous amendment to pages 9, 14 and 17. Applicants respectfully traverse this rejection. Explanation of the support for each of these previously-made amendments follows.

##### *Objection to Previous Modification of Page 9*

As to the previous amendment of paragraph 4 on page 9, The Examiner has misunderstood the structure of compound of Example 25. The compound of Example 25 is "N-[3-(4-benzylidene-1-piperidinyl)propyl]-1-methyl-5-oxo-N-phenyl-3-pyrrolidinecarboxamide hydrochloride". For the Examiner's convenience, the structure of the compound of Example 25 is shown in attached Appendix A. The Examiner has stated that "the compound is N-benzylidene which corresponds to the R<sup>4</sup> group of the formula". However, the benzylidene is *not* R<sup>4</sup>, but rather a substituent for piperidinyl ring formed by R<sup>1</sup> and R<sup>2</sup>. What is more, a structure represented by "N-benzylidene" is not present in the above-mentioned compounds. The Examiner further states that "benzylidene" is a "Ph=C-" group. However, the correct structure of benzylidene is =C-Ph (more precisely =HC-Ph), or



Therefore, Applicants assert that the previous modification to paragraph 4 of page 9 added no new matter to the specification.

##### *Objection to Previous Modification of Page 14*

As to the previous amendment of paragraph 1 on page 14, that amendment aimed at addition of R<sup>4</sup> of the compound of Example 94 into the detailed description of the invention, yet in making the objection, the Examiner erroneously cited the compound of Example 93. Thus, the Examiner is requested to consider the amendment in light of the compound of Example 94. Support for the previous amendment to paragraph 1, page 14 is found on page 5, lines 13 to 14, page 22, lines 3 to 10 and Example 94. For the Examiner's convenience, the structures of compounds of Examples 93 and 94 are shown in attached Appendix A. Therefore, Applicants assert that the previous modification to paragraph 1 of page 14 added no new matter to the specification.

*Objection to Previous Modification of Page 17*

As to the previous amendment of paragraph 3 of page 17, that amendment aimed at addition of an embodiment where  $R^3$  is “aryl optionally having substituent”, the substituent is “hydroxy group optionally having substituent” and the substituent of the hydroxy group is “alkyl substituted with halogen (Example 45) or phenyl (Example 49)” into the detailed description of the invention (as shown in attached Appendix A). However, in view of the Examiner’s objection, Applicants have amended that portion of page 17 again by this amendment. Applicants assert that paragraph 3 of page 17 as amended does not introduce new matter into the specification. By this amendment, the previously objected to material was deleted, and an additional sentence (supported by page 5, lines 1 to 2 and Examples 45 and 49) was added.

Therefore, Applicants respectfully request withdrawal of the objections to the specification.

## **V. Discussion of the 35 U.S.C. Sec. 112, Second Paragraph Rejection of Claim 1**

The rejection of claim 1 under 35 U.S.C. Sec. 112, second paragraph as allegedly vague in the recitation of “hydrocarbon group optionally having a substituent or substituents” has been maintained. Applicants respectfully traverse this rejection.

As an initial matter, Applicants would like once again to draw the Examiner’s attention to the fact that this phrase appears in the description of variables for  $R^3$ ,  $R^4$ , E, Q and R; and that the phrase appears in independent claims 1, 26 and 27; though only claim 1 is subject to this rejection.

Applicants respectfully disagree with the Examiner’s conclusions regarding the previously-provided support for the phrase. The description on page 13, lines 6 to 34 (particularly page 13, line 15) that the Examiner refers to is not an explanation of “hydrocarbon group” but rather an explanation of the *substituents* which the hydrocarbon group may have. As defined in detail by the specification, hydrocarbon groups may have substituents which may be heterocyclic. Applicants find no ambiguity in this.

Moreover, the Examiner has examined and allowed patents including claims reciting hydrocarbon groups which are optionally substituted wherein the optional substituents may be heterocyclic. See U.S. Patent No. 6,548,674 for example.

Therefore Applicants respectfully request withdrawal of the 35 U.S.C. Sec. 112, second paragraph rejection of claim 1.

## **VI. Discussion of the 35 U.S.C. Sec. 112, First Paragraph Rejection of Claim 16**

Claim 16 has been rejected under 35 U.S.C. Sec. 112, first paragraph as allegedly lacking enablement. Applicants respectfully traverse this rejection.

By this amendment, claim 16 has been modified to re-instate the word “pharmaceutical”. In light of the teachings of the specification at page 37, lines 25-32, Applicants believe that their claim is adequately enabled.

Furthermore, the format of this claim is in accordance with the format for composition claims in other U.S. patents which the Examiner has examined and allowed. See for example U.S. Patent No. 6,610,711, claim 40.

Therefore, Applicants respectfully request withdrawal of the 35 U.S.C. Sec. 112, first paragraph rejection of claim 16.

## **VII. Discussion of the 35 U.S.C. Sec. 112, First Paragraph Rejection of Claim 15**

Claim 15 has been rejected under 35 U.S.C. Sec. 112, first paragraph as allegedly not enabled as to the term “pro-drug”. Applicants respectfully traverse the rejection.

As an initial matter, Applicants would like to once again draw the Examiner’s attention to the fact that claims 16 and 25 also contain this term, though only claim 15 is currently under this rejection.

As stated before, Applicants have defined pro-drugs in the specification at page 26, lines 12-33. Therefore the term “pro-drug” is adequately enabled by the specification.

Furthermore, the format of this claim is in accordance with the format for claims which recite prodrugs in other U.S. patents which the Examiner has examined and allowed. See for example U.S. Patent Nos. 6,576,656 and 6,627,645.

Applicants respectfully request withdrawal of the 35 U.S.C. Sec. 112, first paragraph rejection of claim 15.

### **VIII. Discussion of the 35 U.S.C. Sec. 112, First Paragraph Rejection of Claim 28**

The rejection of claim 28 under 35 U.S.C. Sec. 112, first paragraph as allegedly not enabled has been maintained.

Claim 28 does not relate to a method for treating diseases but simply relates to a method for inhibiting CCR5 receptor activity. Accordingly, the effective amount for various cells can be determined easily according to a method analogous to the method of Experimental Example (simply using different cells) and the like, and those of ordinary skill in the art can practice the invention of claim 28 easily given the teachings of the specification. The amount to be administered described on p. 37 is not limited to HIV.

Furthermore, the cited Cohen abstract speaks to cytokines in general, but does not indicate that suppression of CCR5 is highly unpredictable. Therefore Applicants do not believe that this reference supports the Examiner's point very well as applied to method claim 28.

Therefore Applicants respectfully request withdrawal of the 35 U.S.C. Sec. 112, first paragraph rejection of claim 28.

**IX. Discussion of the 35 U.S.C. Sec. 103(a) Rejection over Kato *et al.* in view of Caldwell**

The rejection of claims 1-13, 15, 16 and 30-39 under 35 U.S.C. Sec. 103(a) as allegedly obvious over Kato *et al.*, WO 01/21577 in view of Caldwell, U.S. Patent No. 6,136,827 has been maintained. Applicants respectfully traverse the rejection.

Applicants previously provided a Certified Copy of the translation of the priority document in order to receive the benefit of priority. The Examiner has indicated that the benefit of priority is denied, because she believes that the instant specification and claims are not the same invention as the priority document.

Applicants respectfully disagree with the Examiner – asserting that their invention as set forth in the pending claims as amended is indeed found in the priority document. For example, the compounds of the general formula recited in independent claims 1, 26 and 27 may be found in the translation of the priority document at pages 1 and 2, with the elected linked R<sup>1</sup> and R<sup>2</sup> described on page 12, lines 12-16 of the translation.

Should the Examiner chose to continue to deny the benefit of priority, she is kindly requested to specify which parts of the claims are not supported by the priority document.

Applicants respectfully request reconsideration of the appropriateness of the cited reference as proper art in light of their perfected priority.

**X. Discussion of the 35 U.S.C. Sec. 103(a) Rejection over Kim *et al.* in view of Caldwell *et al.***

The rejection of claims 1-13, 15-24, 26-28 and 30-39 under 35 U.S.C. Sec. 103(a) as allegedly obvious over Kim *et al.*, U.S. Patent No. 6,511,994 in view of Caldwell *et al.*, U.S. Patent No. 6,136,827 has been maintained. Applicants respectfully traverse the rejection.

Applicants previously provided a Certified Copy of the translation of the priority document in order to receive the benefit of priority. The Examiner has indicated that the benefit of priority is denied, because she believes that the instant specification and claims are not the same invention as the priority document.

Applicants respectfully disagree with the Examiner – asserting that their invention as set forth in the pending claims as amended is indeed found in the priority document. For example, the compounds of the general formula recited in independent claims 1, 26 and 27 may be found in the translation of the priority document at pages 1 and 2, with the elected linked R<sup>1</sup> and R<sup>2</sup> described on page 12, lines 12-16 of the translation.

Should the Examiner chose to continue to deny the benefit of priority, she is kindly requested to specify which parts of the claims are not supported by the priority document.

Applicants respectfully request reconsideration of the appropriateness of the cited reference as proper art in light of their perfected priority.

**XI. Discussion of the 35 U.S.C. Sec. 103(a) Rejection over Weber *et al.* in view of Chepkova *et al.* and Patani *et al.***

The rejection of claims 1-16 and 30-39 under 35 U.S.C. Sec. 103(a) as allegedly obvious over Weber *et al.*, U.S. Patent No. 4,891,378 in view of Chepkova *et al.*, Chem Abs. 1991:157055 and Patani *et al.* in Chem. Rev. 1996, 96, 3147-3176 has been maintained. Applicants respectfully traverse the rejection.

By this amendment, E has been limited to trimethylene in the pending claims. Support for this amendment is found in the original claim 13, p. 5, line 22 and Examples 1, 2 to 16, 23 to 70 and 72 to 100.

Applicants' compounds as recited in independent claim 1 as amended, wherein E is limited to trimethylene, cannot be easily envisaged by the skilled in the art from the combined teachings of Weber *et al.* in view of Chepkova *et al.* and Patani *et al.*

Weber *et al.* merely teaches compounds having a structure containing methylene (-CH<sub>2</sub>-) between -N(R<sub>2</sub>)- and the pyrrolidinone ring. Accordingly, the structure of the compound of the present invention as set forth in the claims as amended having trimethylene for E cannot be easily envisaged, even if one skilled in the art was to interchange -CH<sub>2</sub>- of the compound of Weber *et al.* with C=O based on the chemical isostere taught in Chepkova *et al.* and Patani *et al.* In addition, none of the cited references provide motivation to employ a structure wherein E is trimethylene.

The superior CCR5 binding inhibitory effect afforded by the structure of the compound of the present invention is not obvious to the skilled in the art from Weber *et al.* in view of Chepkova *et al.* and Patani *et al.*

Claims 2, 5, 7-9, 11-13, 15, and 16 depend upon claim 1. Applicants assert that the more specific dependent claims are also not rendered obvious by the combined teachings of the cited references for the reason provided above.

Moreover, Applicants submit that the five specific compounds and salts thereof recited in independent claim 14 are neither taught nor suggested by the combined teachings of the cited references.

Claims 3, 4, 6, 10, 30, 31, 33 and 37 have been cancelled.

Claims 32, 34, 36, 38 and 39 depend upon claim 28 (which ultimately depends upon claim 1). Yet since claim 28 is not subject to the present rejection, Applicants respectfully ask the Examiner to reconsider the appropriateness of the rejection of claims 32, 34, 36, 38 and 39.

Therefore Applicants respectfully request withdrawal of the 35 U.S.C. Sec. 103(a) rejection over Weber *et al.* in view of Chepkova *et al.* and Patani *et al.*

## **XII. Conclusion**

Reconsideration of the claims as amended and allowance of pending claims 1, 2, 5, 7-9, 11-16, 25-29, 32, 34-36 and 38-41 is requested.

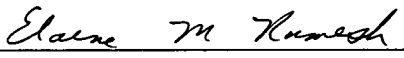
Should the Examiner believe that a conference with Applicants' attorney would advance prosecution of this application, she is respectfully invited to call Applicants' attorney at the number below.

Respectfully submitted,

Dated: February 20, 2004

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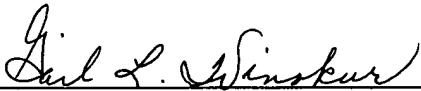
  
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